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# Pharmacological Activities of Cilantro's Aliphatic Aldehydes against *Leishmania donovani*

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## Key words

- *Coriandrum sativum*
- Apiaceae
- essential oil
- (E)-2-decenal
- (E)-2-undecenal
- (E)-2-dodecenal

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## Abstract

Leishmaniasis is a chronic infectious disease caused by different *Leishmania* species. Global occurrences of this disease are primarily limited to tropical and subtropical regions. Treatments are available; however, patients complain of side effects. Different species of plants have been screened as a potential source of new drugs against leishmaniasis. In this study, we investigated the antileishmanial activity of cilantro (*Coriandrum sativum*) essential oil and its main components: (E)-2-undecenal, (E)-2-decenal, (E)-2-dodecenal, decanal, dodecanal, and tetradecanal. The essential oil of *C. sativum* leaves inhibits growth of *Leishmani donovani* promastigotes in

culture with an IC<sub>50</sub> of 26.58 ± 6.11 µg/mL. The aliphatic aldehydes (E)-2-decenal (7.85 ± 0.28 µg/mL), (E)-2-undecenal (2.81 ± 0.21 µg/mL), and (E)-2-dodecenal (4.35 ± 0.15 µg/mL), all isolated from *C. sativum* essential oil, are effective inhibitors of *in vitro* cultures of *L. donovani* promastigotes. Aldehydes (E)-2-decenal, (E)-2-undecenal, and (E)-2-dodecenal were also evaluated against axenic amastigotes and IC<sub>50</sub> values were determined to be 2.47 ± 0.25 µg/mL, 1.25 ± 0.11 µg/mL, and 4.78 ± 1.12 µg/mL, respectively. (E)-2-Undecenal and (E)-2-dodecenal demonstrated IC<sub>50</sub> values of 5.65 ± 0.19 µg/mL and 9.60 ± 0.89 µg/mL, respectively, against macrophage amastigotes. These cilantro compounds showed no cytotoxicity against THP-1 macrophages.

## Introduction

Leishmaniasis is a disease that occurs in many tropical and subtropical areas, causing significant morbidity and mortality in Africa, Asia, and Latin America [1,2]. There are two million new cases annually, and 350 million people are living at risk of being infected [3]. Species of the genus *Leishmania* are protozoan parasites belonging to the family *Trypanosomatidae*. They are the causative agents of human leishmaniasis, which has a reservoir in mammal species and is transmitted by sand flies [3,4].

The treatment of leishmaniasis is difficult due to the intramacrophagic infection form [1]. There are around 25 compounds and formulations useful in the treatment of this disease. Usually, treatments incorporate combinations of amphotericin B, pentamidine, miltefosine, and aminosidine. These drugs have disadvantages such as intravenous administration, long duration of therapy, toxic effects, and high cost [3,5]. Efforts to improve the therapeutic arsenal against this disease have prompted the search for new and less ex-

pensive drugs [6]. Medicinal plants have been investigated as a potential source of new therapeutic compounds with better antileishmanial properties and fewer side effects [7,8].

*Coriandrum sativum* L. (cilantro) belongs to the *Apiaceae* family. The species is cultivated worldwide as a spice, and for its aroma and medicinal properties. The fresh leaves of cilantro are highly regarded by the cuisine of China, Mexico, South America, India, and Southeast Asia [9–11]. The food industry has used cilantro's essential oil for aroma and flavor to mask unpleasant odors of certain foods, due to its distinctive pungent aroma [12,13]. The essential oil found in *C. sativum* leaves is becoming increasingly popular as a functional food and natural preservative agent [14,15].

Earlier investigations have shown cilantro's essential oil antimicrobial properties, namely, antibacterial [10,16], antifungal [17], and antinematocidal [18]. Aliphatic aldehydes, the main constituents of cilantro's essential oil [19], showed inhibitory activity against bacteria and fungi [20]. The aim of this study was to investigate the

antileishmanial activity of cilantro essential oil major compounds.

## Results and Discussion

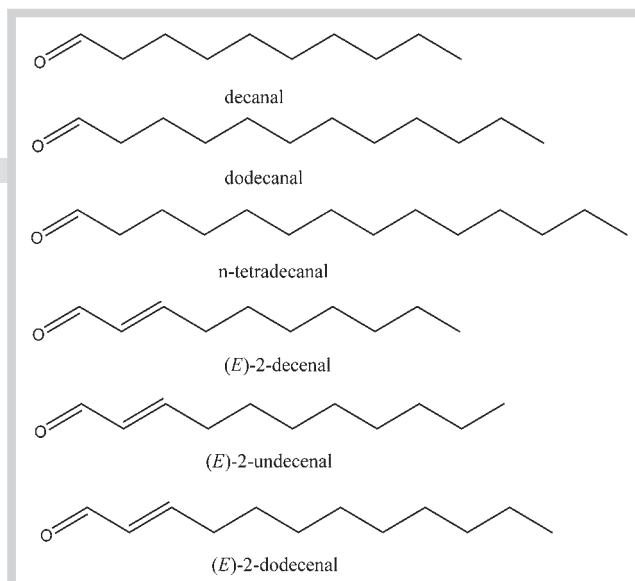
In the present study, cilantro's essential oil had a remarkable effect against *L. donovani* promastigotes *in vitro* with IC<sub>50</sub> and IC<sub>90</sub> values of 26.58 ± 6.11 and 33.03 ± 3.11, respectively (Table 1). As we obtained this result, the essential oil from *C. sativum* leaves was fractionated and three distinct fractions were obtained. One of the fractions (fraction 2) had IC<sub>50</sub> and IC<sub>90</sub> values approximately 2.0 and 1.5 times lower than cilantro essential oil, respectively, suggesting the presence of a bioactive constituent(s) (Table 1). Using the GC/MS and GC retention indices technique, it was possible to identify the main constituents of the active fraction 2 as aldehydes with linear chains ranging from 10 to 14 carbon atoms. The major aliphatic aldehydes found were decanal, dodecanal, tetradecanal, (*E*)-2-decenal, (*E*)-2-undecenal, and (*E*)-2-dodecenal (Fig. 1). Aliphatic aldehydes found in the active fraction are well-known as major compounds in cilantro essential oil [12, 19]. Since the active fraction had aliphatic aldehydes, the commercially available standards decanal, dodecanal, tetradecanal, (*E*)-2-undecenal, (*Z*)-8-undecenal, (*Z*)-4-decenal, (*Z*)-7-decenal, (*E*)-2-decenal, and (*E*)-2-dodecenal were purchased and all tested against *L. donovani* promastigotes. The results showed that (*E*)-2-undecenal had the lowest IC<sub>50</sub> and IC<sub>90</sub> values (2.81 ± 0.21 µg/mL and 4.71 ± 0.21 µg/mL, respectively) followed by (*E*)-2-dodecenal, (*E*)-2-decenal, tetradecanal, and dodecanal (Table 2). Decanal and the isomers of (*E*)-2-undecenal [(*Z*)-8-undecenol] and (*E*)-2-decenal [(*Z*)-4-decenal and (*Z*)-7-decenol] had no activity against *L. donovani* promastigotes (Table 2). Dose-response curves against *L. donovani* promastigotes for dodecanal, tetradecanal, (*E*)-2-decenal, (*E*)-2-undecenal, and (*E*)-2-dodecenal, as well as for the drug controls pentamidine and amphotericin B, are shown in Fig. 2.

In a second stage, (*E*)-2-alkenals were evaluated against axenic amastigotes and macrophage amastigotes of *L. donovani*. (*E*)-2-decenal, (*E*)-2-undecenal, and (*E*)-2-dodecenal were highly active against axenic amastigotes (Table 3) with IC<sub>50</sub> values of 2.47 ± 0.25 µg/mL, 1.25 ± 0.11 µg/mL, and 4.78 ± 1.12 µg/mL, respectively (Fig. 3). All three compounds were also evaluated against macrophage amastigotes, and while (*E*)-2-decenal was inactive, (*E*)-2-undecenal and (*E*)-2-dodecenal demonstrated IC<sub>50</sub> values of 5.65 ± 0.19 µg/mL and 9.60 ± 0.89 µg/mL, respectively (Fig. 4). When these compounds were tested for cytotoxicity, they showed no toxicity to THP-1 macrophages (Table 3). To our knowledge, this is the first report on the antileishmanial properties of cilantro's essential oil and its major compounds. There are, however, reports on the effectiveness of cilantro oil as an antimicrobial agent, acting against bacteria, fungi, and nematodes [12, 16–18] but not against *Leishmania* sp. Some studies have demonstrated that aliphatic aldehydes from cilantro's essential oil (alkanals and alkenals) have antibacterial and antifungal properties [20, 21].

Although our study does not explain the mechanism of how aliphatic aldehydes kill *Leishmania* sp., Fujita and Kubo [21] carried out a mode of action study of such aldehydes on fungi and bacteria. They reported that alkanals and alkenals disrupt microbial cell membranes. This capacity is correlated with the hydrophobic alkyl chain length from the hydrophilic aldehyde group. The activity related to the length of the carbon chain in the molecule

**Table 1** *In vitro* activity of cilantro's essential oil and its fractions against *L. donovani* promastigotes.

	<i>L. donovani</i> IC <sub>50</sub> (µg · mL <sup>-1</sup> )	<i>L. donovani</i> IC <sub>90</sub> (µg · mL <sup>-1</sup> )
Essential oil	26.58 ± 6.11	33.03 ± 3.11
Fraction 1	NA*	NA
Fraction 2	13.57 ± 2.12	22.76 ± 1.91
Fraction 3	NA	NA
Pentamidine	0.73 ± 0.06	1.92 ± 0.12
Amphotericin B	0.13 ± 0.01	0.24 ± 0.02

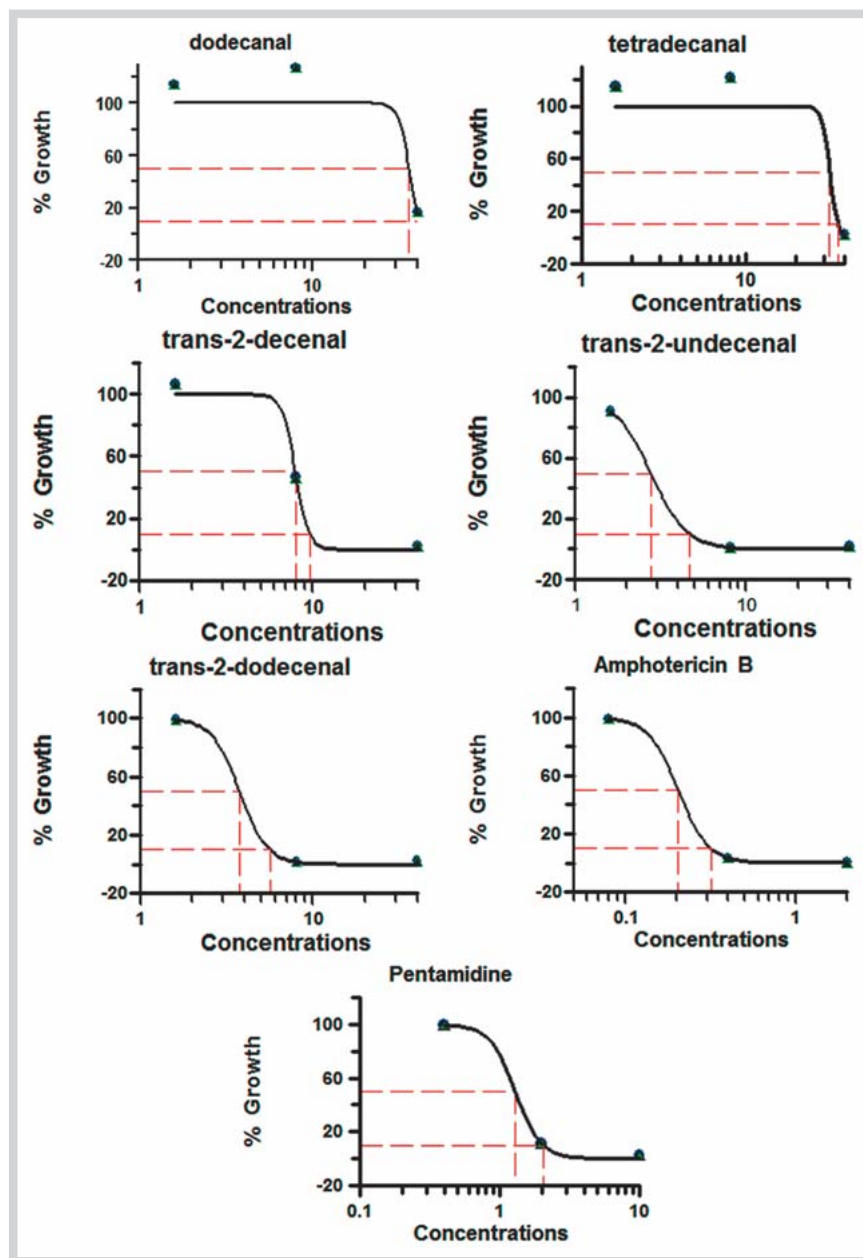


**Fig. 1** Structures of aliphatic aldehydes isolated from cilantro essential oil: decanal, dodecanal, tetradecanal, (*E*)-2-decenal, (*E*)-2-undecenal, and (*E*)-2-dodecenal.

**Table 2** *In vitro* activity of the compounds present in cilantro's essential oil and structural analogs against *L. donovani* promastigotes.

Compound	<i>L. donovani</i> IC <sub>50</sub> (µg · mL <sup>-1</sup> )	<i>L. donovani</i> IC <sub>90</sub> (µg · mL <sup>-1</sup> )
<b>Alkanals</b>		
Decanal	NA	NA*
Dodecanal	35.81 ± 3.11	NA
Tetradecanal	32.00 ± 2.12	36.41 ± 3.15
<b>Alkenals</b>		
( <i>E</i> )-2-decenal	7.85 ± 0.28	10.04 ± 0.07
( <i>Z</i> )-4-decenal	NA	NA
( <i>Z</i> )-7-decenal	NA	NA
( <i>E</i> )-2-undecenal	2.81 ± 0.21	4.71 ± 0.21
( <i>Z</i> )-8-undecenal	NA	NA
( <i>E</i> )-2-dodecenal	4.35 ± 0.15	5.97 ± 0.23
Pentamidine	1.12 ± 0.09	2.11 ± 0.22
Amphotericin B	0.16 ± 0.01	0.32 ± 0.02

\* NA = no activity; values are the means of two independent experiments. IC<sub>50</sub> and IC<sub>90</sub> values were computed from the dose-response curves (Fig. 2) with ExcelFit®. Pentamidine and amphotericin B are drug controls



**Fig. 2** Dose-response curves for dodecanal, tetradecanal, (*E*)-2-decenal, (*E*)-2-undecenal, and (*E*)-2-dodecenal and for drug controls pentamidine and amphotericin B against *L. donovani* promastigotes. (Color figure available online only.)

**Table 3** Activity of (2*E*)-alkenals against axenic amastigotes, macrophage amastigotes, and cytotoxicity in transformed THP-1 cells.

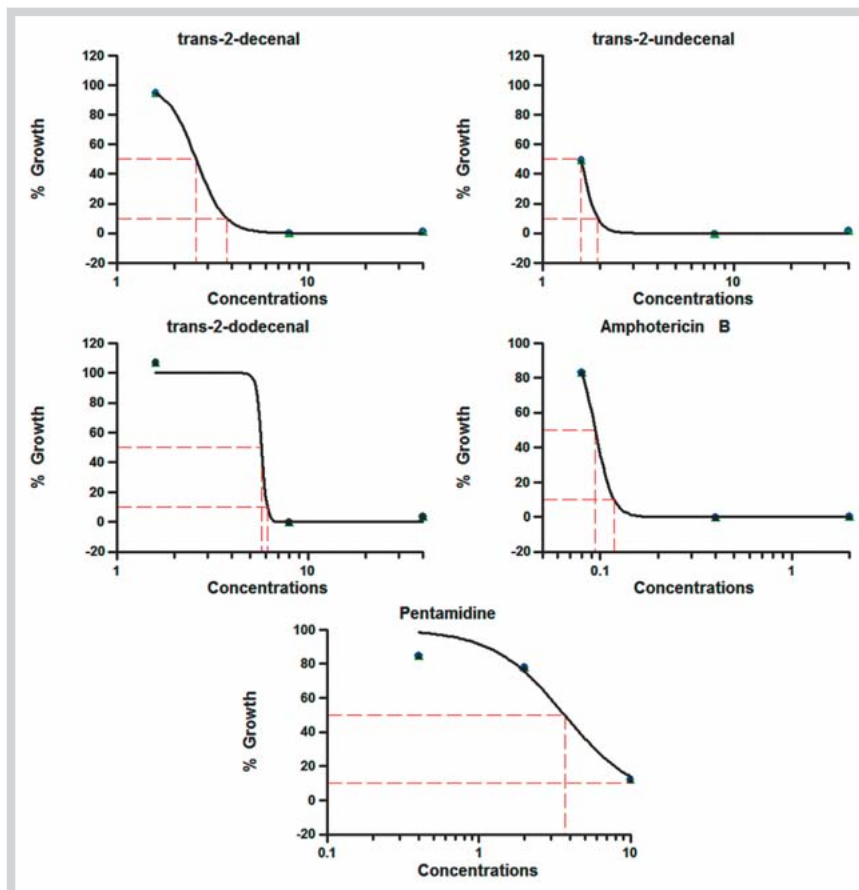
Compound	Axenic amastigotes		Macrophage amastigotes		Cytotoxicity (transformed THP-1 cells)	
	IC <sub>50</sub>	IC <sub>90</sub>	IC <sub>50</sub>	IC <sub>90</sub>	IC <sub>50</sub>	IC <sub>90</sub>
( <i>E</i> )-2-decenal	2.47 ± 0.25	3.49 ± 0.21	> 10	> 10	> 10	> 10
( <i>E</i> )-2-undecenal	1.25 ± 0.11	2.07 ± 0.24	5.65 ± 0.19	> 10	> 10	> 10
( <i>E</i> )-2-dodecenal	4.78 ± 1.12	5.2 ± 0.63	9.60 ± 0.89	> 10	> 10	> 10
Pentamidine	3.69 ± 0.21	> 10	0.40 ± 0.03	2.40 ± 0.16	> 10	> 10
Amphotericin B	0.09 ± 0.02	0.12 ± 0.12	0.53 ± 0.10	1.89 ± 0.12	> 10	> 10

Values given are µg/mL and are the mean of two independent experiments. IC<sub>50</sub> and IC<sub>90</sub> values were computed from the dose-response curves (● Fig. 3 and 4) with ExcelFit. Due to limitations with the solvent DMSO, the compounds used in this assay could be tested only up to the maximum concentration of 10 µg/mL. Pentamidine and amphotericin B are drug controls

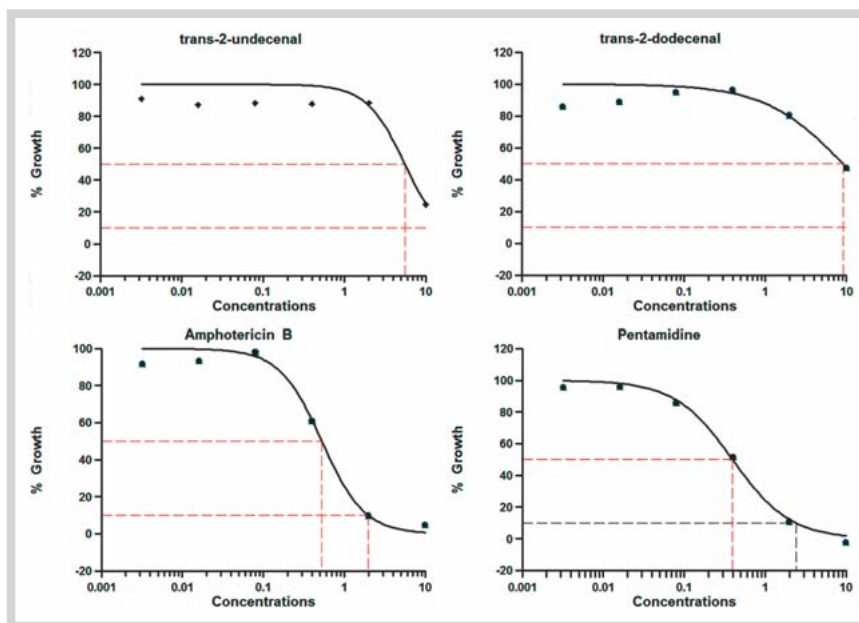
depends on the microorganism and its form. For *Salmonella choleraesuis*, the activity increased with the increasing carbon chain length up to (*E*)-2-dodecenal [20].

An alternative explanation for explaining the mode of action may be that these aliphatic aldehydes are simply acting as electrophilic species. Aldehydes have been reported to react with biological amino groups to form Schiff bases. Similarly,  $\alpha,\beta$ -unsatu-





**Fig. 3** Dose-response curves for (E)-2-decenal, (E)-2-undecenal, and (E)-2-dodecenal and for drug controls pentamidine and amphotericin B against *L. donovani* axenic amastigotes. (Color figure available online only.)



**Fig. 4** Dose-response curves for (E)-2-undecenal and (E)-2-dodecenal and for drug controls pentamidine and amphotericin B against THP-1 macrophage-*L. donovani* amastigotes. (Color figure available online only.)

rated aldehydes are also electrophilic and may undergo Michael additions with biological nucleophiles [22, 23]. In our case, leishmania forms responded differently to aliphatic aldehydes. For *L. donovani* promastigotes, (E)-2-undecenal was more efficient, followed by (E)-2-dodecenal and (E)-2-decenal. Against axenic amastigotes, (E)-2-undecenal was also more effective, followed by (E)-2-decenal and (E)-2-dodecenal.

The antileishmanial potential of essential oil preparations from different sources has been previously reported. The treatment on BALB/c mice infected with *L. amazonensis* with essential oil preparations from *Chenopodium ambrosioides* caused a significant inhibition of cutaneous lesion formations. However, its major components, namely, ascaridole, carvacrol, and caryophyllene oxide, did not show any effect [24]. Inhibition of mitochondrial

functions was suggested as the potential mechanism for leishmaniacidal action of *C. ambrosioides* essential oil preparations [25]. The essential oil preparation from *Bixa orellana* seeds showed activity against the intracellular amastigote form ( $IC_{50} = 8.5 \mu\text{g/mL}$ ) of *L. amazonensis*, while the cytotoxic concentration was sevenfold higher for the host cells [26].

Our study showed that alkenals (*E*)-2-decenal, (*E*)-2-undecenal, and (*E*)-2-dodecenal were more effective against *L. donovani* promastigotes than alkanals (decanal, dodecanal, and tetradecanal). The results may be explained by double bonds present in alkenals, since this characteristic is associated with enhancement of the antimicrobial property (Kubo et al. [20]) and for the reasons mentioned above. The results showed that the essential oil of *C. sativum* leaves and its major compounds may represent a valuable source of new drugs against leishmaniasis.

## Materials and Methods

### Essential oil isolation

The fresh herb cilantro (2.0 kg) was purchased in a retail store in Oxford, MS, transported to the laboratory in the Natural Products Utilization Research Unit – USDA-ARS, where healthy leaves were selected. An authentic specimen has been retained in the National Center for Natural Products Research, ID# MAD1-002. The sample was authenticated by Dr. Charles L. Cantrell, Research Chemist, USDA-ARS. Leaves were cut and placed into a 1-L round-bottom flask followed by the addition of 300 mL of deionized water. Fresh leaves were subjected to hydrodistillation for 90 min [27]. Hydrodistillation was performed using a Clevenger apparatus containing 10 mL of *n*-pentane. The organic layer of the four distillations was combined and dried under a stream of dry nitrogen, resulting in a yield of 500 mg.

### Fractionation of the essential oil

The essential oil (500 mg) was fractionated using a Biotage XP-Sil, 100 g, SNAP cartridge (40–63  $\mu\text{m}$ , 60 Å, 40 × 150 mm) running at 40 mL·min<sup>-1</sup> using a hexane:acetone step gradient beginning with 100:0 to 0:100 over 2200 mL followed by 0:100 over 600 mL. Twenty-two mL portions were collected in 16 × 150 mm test tubes. Based on TLC similarities, the content of the tubes were combined providing four fractions with the following yields: **1** – 2.1 mg; **2** – 51.0 mg; **3** – 34.0 mg.

### Analysis by gas chromatography–mass spectrometry

The essential oil and fractions were analyzed by GC-MS on a Varian CP-3800 GC coupled to a Varian Saturn 2000 MS/MS. The GC was equipped with a CP Sil 8 CB capillary column (30 m × 0.25 mm, with film thickness of 0.25  $\mu\text{m}$ ) operated using the following conditions: injector temperature, 240 °C; column temperature, 60–240 °C at 3 °C/min then held at 240 °C for 5 min; carrier gas, He; injection volume, 1  $\mu\text{L}$ , split, 50:1. The MS mass ranged from 40 to 650  $m/z$ . There was a filament delay of 5 min, target TIC of 30000, a prescan ionization time of 100  $\mu\text{s}$ , an ion trap temperature of 150 °C, manifold temperature of 60 °C, and a transfer line temperature of 170 °C.

Essential oil constituents were each identified by first determining their retention index using previously reported methods and comparison of mass spectrum with that reported by Adams [28]. Final confirmation was accomplished by comparison of retention times and mass spectra data with authentic standards.

## Chemicals

Commercial standards (*E*)-2-decenal (>92% purity), (*Z*)-4-decenal (>90% purity), (*Z*)-7-decenal (>96% purity), (*E*)-2-undecenal (>95% purity), (*Z*)-8-undecenal (>96% purity), (*E*)-2-dodecenal (>93% purity), decanal (>98% purity), and dodecanal (>93% purity) were purchased from Sigma-Aldrich. Tetradecanal (>95% purity) was purchased from BOC Sciences. The standard antileishmanial drugs pentamidine isothionate salt (98% purity) (P0547) and amphotericin B from *Streptomyces* (98% purity, A4888) were procured from Sigma Chemicals Co.

### In vitro assay for antileishmanial activity

The *in vitro* antileishmanial assay was done on a culture of *L. donovani* promastigotes and axenic amastigotes by the Alamar Blue assay [29]. The promastigotes culture was maintained at 26 °C in RPMI 1640, pH 7.4 with 10% FBS. The axenic amastigotes were cultured at 37 °C and 5% CO<sub>2</sub> in RPMI-1640 supplemented with 4-morpholineethanesulfonic acid (MES) (4.88 g·L<sup>-1</sup>), L-glutamine (298.2 mg·L<sup>-1</sup>), adenosine (26.7 mg·L<sup>-1</sup>), folic acid (10.1 mg·L<sup>-1</sup>), BME vitamin mix, sodium bicarbonate (352.8 mg·L<sup>-1</sup>), and 10% FBS. The pH of the culture medium was 5.5. In a 96-well microplate, the samples with the appropriate dilution were added to the leishmania promastigotes/axenic amastigote culture (2 × 10<sup>6</sup> cell mL<sup>-1</sup>). The compounds were tested at six concentrations ranging from 40 to 0.0128  $\mu\text{g} \cdot \text{mL}^{-1}$ . The plates were incubated for 72 h at 26 °C and 37 °C, respectively, for promastigotes and axenic amastigotes. The growth of leishmania promastigotes/amastigotes was determined.  $IC_{50}$  and  $IC_{90}$  values were computed from the dose-response curves.

### In vitro macrophage amastigote assay

A recently developed promastigote rescue assay was used [30]. The THP-1 cells (human acute monocytic leukemia cell line) were maintained in RPMI 1640 medium supplemented with 10% FBS. The cells were prepared prior to each assay and suspended in RPMI 1640 medium with 10% FBS at the cell density of 2.5 × 10<sup>5</sup> cells mL<sup>-1</sup>. Phorbol-12-myristate-13-acetate (PMA) was added to the cell suspension to achieve a final concentration of 25 ng·mL<sup>-1</sup>, and cells were seeded onto a clear flat-bottom 96-well plate with 200  $\mu\text{L}$  (5 × 10<sup>4</sup> cells) into each well. The plate was incubated in a 5% CO<sub>2</sub> incubator at 37 °C for at least 12 h for differentiation of the THP-1 cells to adherent macrophages. After overnight incubation, the medium from each well was discarded and adherent cells were gently washed at least twice with serum free RPMI 1640 medium. The *L. donovani* promastigotes culture was harvested at the stationary phase (metacyclic infective stage) and suspended into RPMI 1640 medium with 2% FBS at a density of 2.5 × 10<sup>6</sup> cells mL<sup>-1</sup>. Two hundred  $\mu\text{L}$  of promastigotes (5 × 10<sup>5</sup>) culture was added to each well. The plate was further incubated in a 5% CO<sub>2</sub> incubator at 37 °C for at least 24 h to allow the infection of macrophages with the leishmania parasites. After 24 h, the non-adherent macrophages and unattached leishmania promastigotes were washed off with serum free RPMI 1640 medium. The infected macrophages were further incubated at 37 °C and 5% CO<sub>2</sub> in 200  $\mu\text{L}$  RPMI 1640 medium and 2% FBS with different concentrations of standard antileishmanial drugs (pentamidine and amphotericin B) or the test compounds for 48 h. The control wells with medium, uninfected THP-1 cells, and infected cells without drugs or test compounds were also set up simultaneously. The cultures were washed off with serum free RPMI 1640 and treated for 30 s with 20  $\mu\text{L}$  of 0.05% sodium dodecyl sulfate in RPMI 1640 medium for the release of amastigotes from the infected macro-

phages. To each well, 180  $\mu$ L of RPMI 1640 medium with 10% FBS was added, and the plate was further incubated at 26 °C for 48 h to allow the transformation of released amastigotes to promastigotes. To each well, 20  $\mu$ L of Alamar Blue was added; the plates were incubated at 26 °C for 24 h and read on a BMG Fluostar microplate reader (BMG Lab Technologies) at an excitation wavelength of 544 nm and an emission wavelength of 590 nm. Each compound was tested in duplicate at six concentrations; IC<sub>50</sub> and IC<sub>90</sub> values were computed from the dose-response curves.

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## Conflict of Interest

The authors declare no conflict of interest.

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